REMARKS

Claims 1-4, 6-7, 10, and 16-28 were pending in the present application. Claim 1 has been amended herein to eliminate variables no longer recited in the claim. Claim 24 has been amended to correct a typographical error. Claims 10, 16-23, and 26-28 have been canceled herein without prejudice to their presentation in another application. No new matter has been added. Upon entry of the present amendment, claims 1-4, 6-7, 24, and 25 will remain pending.

I. The Claimed Invention Is Not Obvious

Claims 1-4, 6, 7, 24, and 25 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,620,989 (hereinafter, the "Harrison reference") and Stevenson et. al., J. Med. Chem., 1998, 41, 4623-4635 (hereinafter the "Stevenson reference") in view of Bernstein et al., Bioorg. Med. Chem. Lett., 2001, 11, 2769-2773 (hereinafter the "Bernstein reference") and Elliott et. al., Bioorganic & Med. Chem. Lett., 2002, 12, 1755-1758 (hereinafter, the "Elliott reference"). Applicants traverse the rejection and respectfully request reconsideration thereof.

The Office asserts that "it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of Harrison and Stevenson et. al. to produce the instant invention" (see, Office Action at page 12). The Office further asserts that the analogs differ "only in the substitution of phenyl for naphthyl" and the "use of a different linker between the piperidine ring and the phenyl group" (see, Office Action at page 12). The Office further asserts that the Bernstein reference shows "the preference for naphthyl over phenyl" and that "Elliott et. al. in his NK-1 antagonists replaced amino groups with amides and they were all 'tolerable'" (see, Office Action at page 13). Thus, the Office Action concludes that it would have been *prima facie* obvious to: 1) make the compounds of either the Harrison or Stevenson references, 2) replace the phenyl group with a napthyl group, and 3) further replace the linker between the piperidine ring and the phenyl group (e.g., $-CH_2-O-CH_2-$ linker of the Harrison reference and the $-CH_2-NH-CH_2-$ linker of the Stevenson reference) with an amide linker.

As a preliminary matter, Applicants' undersigned representative is unable to locate the structure recited at page 11 of the Office Action allegedly disclosed by the Bernstein reference.

The Office fails to make out a *prima facie* case of obviousness. When making a *prima facie* case of obviousness, it remains necessary to identify some reason that would have led a person skilled in the art to modify the teachings of a reference in a particular manner. *Takeda Chemical Industries, Ltd. v Alphapharm Pty. Ltd.*, 492 F.3d 1350, 83 USPQ.2d 1169 (Fed. Cir. 2007). No such reasoning has been provided. Applicants respectfully point out that "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ.2d 1780, 1784 (Fed. Cir. 1992).

Regarding the replacement of a phenyl group with a naphthyl group, the Office overly simplifies and greatly expands what is reported in the Bernstein reference. The Bernstein reference does not teach or suggest that any phenyl group on any NK-1 antagonist can be replaced with a naphthyl group. Rather, the Bernstein reference reports structural modifications on two NK_2 selective antagonists, SR48968 and ZD7944. In particular, ZD7944 was modified by substitution of a naphthamide moiety to yield compound 2a (see, Table 1 of the Bernstein reference). When this naphthamide-modified ZD7944 compound (e.g., compound 2a) was further modified to create compounds 2b through 2p (by replacement of various substituted piperidines), the activities of the resultant compounds changed. Indeed, the Bernstein reference teaches that "[k]eeping the naphthamide constant we explored a larger group of piperidines and found that only the corresponding sulfone **2h** and the pyridyl **2m** analogues retained good dual activity. The other piperidine groups led to loss of activity at the NK_1 receptor or at both the NK_1 and NK_2 receptors" (see, Bernstein reference at page 2770, left column, end of first paragraph). Thus, 13 of the 15 analogues rteported in Table 1 of the Bernstein reference had less activity at the NK_1 receptor when the piperidine moiety of ZD7944 was modified. Indeed, one of skill in the art would conclude that to retain activity of a naphthamide-modified NK_1 antagonist, one should prepare the sulfone or pyridyl analogues.

Rather, one of ordinary skill in the art would, after examining the Bernstein reference, conclude that replacement of the specific piperidine group of an NK_2 antagonist (e.g., ZD7944)

with other various piperidine groups, despite the presence of the naphthamide group, can lead to a loss of activity. Thus, retention of NK_1 receptor activity upon replacing a phenyl group with a naphthyl group depends upon the structure remaining in the rest of the compound. Indeed, 13 of 15 analogues containing a naphthamide group lost NK_1 receptor activity upon altering the piperidine group remaining in the rest of the compound.

Regarding the replacement of the linker between the piperidine ring and the phenyl group (e.g., $-CH_2-O-CH_2-$ linker of the Harrison reference and the $-CH_2-NH-CH_2-$ linker of the Stevenson reference) with an amide linker, the Office again overly simplifies and greatly expands what is reported in the Elliott reference. The Elliott reference does not teach or suggest that any linker group on any NK-1 antagonist can be replaced with an amide linker. Table 1 of the Elliott reference reports different linkers within a structural framework of a compound that is quite distinct from that of Applicants' claimed compounds. Indeed, the Office fails to provide any evidence that the compound depicted in Table 1 of the Elliott reference is an analogue of Applicants' claimed compounds and, thus, any change in the compound of the Elliott reference would be expected to also be appropriate for Applicants' claimed compounds. Thus, simply because a particular linker within one compound may work does not mean that the same linker within a different compound having a distinct structure would also work.

Even when one skilled in the art examines the linkers in Table 1 of the Elliott reference, there is no reason for a person skilled in the art to modify the already naphthamide-modified Stevenson and/or Harrison compounds to include the linkers of the Elliott reference. The Elliott reference teaches "A number of different linkers are tolerated, most notably the amides **2** and **15**, the ammine **17** and the ether **23**. The relatively poor affinity of the propyl linker **24** … shows that a heteroatom in the chain is beneficial. This could be because the heteroatom introduces a conformational bias which favours binding, or due to participation of the heteroatom in a hydrogen bond to the receptor" (see, Elliott reference at page 1757, left column, first paragraph). Applicants point out that the Stevenson compounds have an amine linker and the Harrison compounds have an ether linker, both of which are noted by the Elliott reference as being "tolerated." There is no reason, other than Applicants' specification, to replace one tolerated linker with another tolerated linker. Indeed, the linkers of the Stevenson and Harrison references

already have a heteroatom. The Office's reasoning is more supportive of compounds having the propyl linker, which is not the present case. Further, even if one skilled in the art had reason to select an amide linker (and Applicants submit that such is not the case), the Elliot reference reports that "amides **2** and **15**" are tolerated. Applicants' claimed compounds do not comprise "amides **2** and **15**." Rather, Applicants' claimed compounds have an amide that more closely resembles amide 13 of the Elliott reference. Noticeably absent from the Elliott authors' conclusion of tolerated linkers is amide 13. Thus, one skilled in the art having examined the Elliott reference in its entirety would have no reason to further modify the already naphthamide-modified Stevenson and/or Harrison compounds to include the "tolerated" linkers of the Elliott reference. Further, even if such modification using the "tolerated" linkers of the Elliott reference were carried out, Applicants' claimed compounds are still not produced.

Thus, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

II. Obviousness-Type Double Patenting

Claims 1-4, 6, 7, 10, and 16-28 are provisionally rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-13 of co-pending application Serial No. 10/539,140 (hereinafter, the "'140 application") in view of the Elliot reference. In addition, claims 1-4, 6, 7, 10, and 16-28 are also provisionally rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-12 of co-pending application Serial No. 10/527,280 (hereinafter, the "'280 application") in view of the Elliot reference. Applicants traverse these rejections and respectfully request reconsideration thereof.

An obviousness-type double patenting rejection is analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. §103. *In re Braithwaite*, 154 U.S.P.Q. 29, 34 (C.C.P.A. 1967) and *In re Longi*, 225 U.S.P.Q. 645, 648 n.4 (Fed. Cir. 1985). Thus, under the law, the pivotal question in an obviousness-type double patenting analysis is: Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the

patent? *In re Vogel*, 164 U.S.P.Q. 619 (C.C.P.A. 1970). If the answer to this question is no, there can be no double patenting. In making this analysis, then, the proper inquiry is as taught in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). See, M.P.E.P. §804.

Again, as stated above, one skilled in the art having examined the Elliott reference in its entirety would have no reason to further modify the compounds of the '140 application to replace an amine linker (e.g., one of the "tolerated" linkers of the Elliott reference) or the compounds of the '280 application to replace an ether linker (e.g., one of the "tolerated" linkers of the Elliott reference) with one of the "tolerated" amide linkers of the Elliott reference. Further, even if one skilled in the art had reason to select an amide linker (and Applicants submit that such is not the case), the Elliot reference reports that "amides **2** and **15**" are tolerated. Applicants' presently claimed compounds do not comprise "amides **2** and **15**." Thus, one skilled in the art having examined the Elliott reference in its entirety would have no reason to further modify the compounds of the '140 application or the compounds of the '280 application to include the "tolerated" amide linkers of the Elliott reference. Further, even if such modification using the "tolerated" linkers of the Elliott reference were carried out, Applicants' presently claimed compounds are still not produced.

Thus, the presently claimed compounds are not obvious variants of the compounds recited in the '140 and '280 applications. Accordingly, Applicants respectfully request that the obviousness-type double patenting rejections be withdrawn.

III. The Claimed Invention Is Enabled

Claims 10, 16-23, and 26-28 are rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to meet the enablement requirement regarding use of the claimed invention. Although Applicants disagree with the reasoning set forth in the Office Action to support the enablement rejection, solely to advance prosecution of the present application, claims 10, 16-23, and 26-28 have been canceled herein without prejudice to their presentation in another application. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

IV. Conclusion

Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at 610.640.7854 to resolve any remaining issues.

The Commissioner is hereby authorized to debit any underpayment of fee due or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

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